REMARKS

I. **Status of the claims**

Claims 9-20 and 22-38 are currently pending. Claims 10 and 20 were amended to correct typographical errors.

II. **35 U.S.C.112, First Paragraph Rejections**

A. **Written Description Rejection**

Reconsideration is requested of the rejection of claims 9-20 and 22-38 for failing to comply with the written description requirement.

Claim 9 is directed towards a composition comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibitor, a 5-lipoxygenase inhibitor and an immunosuppressive drug selected from antiproliferation agents, antiinflammatory acting compounds and inhibitors of leukocyte activation. Claim 20, the other independent claim, is directed towards a pharmaceutical composition comprising a therapeutically-effective amount of a 5-lipoxygenase inhibitor, a cyclosporin compound and a cyclooxygenase-2 inhibitor selected from Dupont Dup 697, Taisho NS-398, meloxicam, flosulide and compounds of Formula I or a pharmaceutically acceptable salt of a compound having Formula I.

Applicants note that to satisfy the written description requirement, the specification need only convey "with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." MPEP § 2163.02; *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). (Emphasis added.)

Furthermore, as stated in MPEP 2163:

> Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v.*

Wells Elecs., Inc., 525 U.S. 55, 68, 119, S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406, *Amgen, Inc. v. Chugai Pharmaceutical* , 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). (Emphasis added.)

Furthermore, MPEP §2163(II)(3)(a)(ii) specifically dictates:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e, structure or other physical and /or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In this case, the common attribute possessed by one of the compounds recited in claim 9 is its ability to inhibit cyclooxygenase-2 in a selective manner, and the common attribute possessed by the second compound is its ability to inhibit 5-lipoxygenase in a selective manner. The third compound is an immunosuppressive drug which is an antiproliferating agent, an antiinflammatory or a leukocyte activation inhibitor. The present specification describes structural characteristics of suitable compounds for use in claims 9 and 20, and lists numerous COX-2 inhibitors, 5-LO inhibitors, and immunosuppressive drugs. In addition, the specification describes the functional characteristics of COX-2 inhibitors and 5-LO agents.

In terms of structure, the specification recites that the cyclooxygenase-2 inhibitor is selected from meloxicam, flosulide and a class of sulfonamides or methylsulfonyls compounds having formula I. See pages 12, and 15-18 of the specification. The specification further discloses 13 examples of compounds having formula I. See pages 17-18 of the specification. According to the specification, any one of reaction schemes I-X may be utilized to prepare a cyclooxygenase-2 inhibitor having formula I.

In terms of function, the specification defines a cyclooxygenase-2 inhibitor as:

> ...compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

See page 12, lines 5-16, of the specification.

Similarly, the specification recites both functional and structural features of suitable 5-LO inhibitors for use in the claim 9 composition. In terms of structure, pages 13-14 of the specification disclose well over 150 examples of publically available compounds having the recited function (i.e., selective 5-LO inhibition). In terms of function, the specification defines a 5-LO inhibitor as "compounds which selectively inhibit 5-lipoxygenase with an IC_{50} of less than about 10 μM. More preferably, the 5-lipoxygenase inhibitors have an IC_{50} of less than about 1 μM." See page 12, lines 17-21 of the specification.

In addition, the specification discloses a number of classes of immunosuppressants that may be employed in the combination of claim 9 along with examples of specific compounds belonging to each class. In particular, the specification states the immunosuppressant may be an antiproliferative agent, antiinflammatory-acting compound or an inhibitor of leukocyte activation selected from the following compounds:

> ...a cyclosporin compound, or Fujisawa FK-506 (macrolide lactone) compound, or rapamycin, or a glucocorticoid, or an antiproliferative agent, or a monoclonal antibody such as an anti-CD3 (anti-T cell receptor antibody) or anti-CD5/7 or anti-CD4 agent, or an anti-IL-2 receptor (anti-cytokine receptor type antibody) agent, or an anti-IL-2 (anti-cytokine antibody), or Nippon NKT-01 (15-deoxyspergualin) or Syntex RS-61443.

See pages 11-12 of the specification.

Thus, Applicants have described distinguishing identifying characteristics sufficiently to show that the applicant was in possession of the claimed invention

The Office alleged that the specification does not disclose the structure or physical properties of **all** the drugs that are required to practice the instant invention. Applicants submit that patent applicants are **not required** to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general knowledge of the art would enable one of ordinary skill in the art to make and use the invention. In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970).

The Office further stated that the instant claims do not disclose structures or identities of compounds that are COX-2 inhibitors, 5-lipoxygenase inhibitors or immunosuppressive drugs within the same claim. Applicants respectfully disagree and turn the Examiner's attention to dependent claims 10-19 and 22-38, which detail identities of COX-2 inhibitors, 5-lipoxygenase inhibitors and immunosuppressive drugs that may be used together, i.e., within the same claim. Moreover, each of claims 10-20 and 23-38 require COX-2 inhibitors, 5-LO inhibitors, and immunosuppressants having a recited chemistry such that a skilled artisan could make or use the composition in each of these claims without undue experimentation.

Applicants further note that case law is replete with examples where claims directed toward a combination of two or more compounds were found to satisfy the written description requirement when one or more of the compounds were described only functionally. By way of example, *in re Fuetterer*, the inventor claimed a composition for use in the production of rubber tires where one component of the composition was described only functionally as an "inorganic salt that is capable of holding a mixture of said protein and/or carbohydrate in colloidal suspension." 319 F.2d 259, 138 USPQ 217 (1963). The Examiner rejected the inventor's claims as not satisfying the written description requirement, stating that "it is well established that claims should set out what the materials are and not by what they do." Id at 262. The CCPA reversed the rejection, holding that it is permissible to use only terms of effect or

result to the extent that the terms accurately describe essential qualities of a product to one skilled in the art. Id at 264. According to the court, the essential qualities of the inorganic salt were sufficiently described solely by its ability to maintain other components of the composition in "colloidal suspension." Id at 264-265.

In *In re Herschler*, the inventor claimed a combination comprising dimethyl sulfoxide (DMSO) and "a physiologically active steroidal agent" for use in enhancing penetration across a membrane and claimed priority dating back to the filing of a great-grandparent application. 591 F.2d 695, 200 USPQ 711 (1979). The Examiner rejected the claims in view of prior art published after the filing date of the great-grandparent application stating in part that the claims were not entitled to the great-grandparent's filing date because the great-grandparent application lacked written description to support "a physiologically active steroidal agent" in view of disclosure of only 1 example (corticosteroid) to support the genus. Id at 696. The CCPA reversed the rejection, holding that "the **use of known** chemical compounds in a manner auxiliary to the invention must have a corresponding written description **only so specific as to lead one having ordinary skill in the art to that class of compounds**." Id at 702 (emphasis added). According to the court, steroids as a class of compounds when employed in a composition with DMSO are chemically similar. Id at 701.

Analogous to the combination of *In re Fuetterer*, the combination of claim 9 describes "essential qualities" of each component of the combination to a skilled artisan. The cyclooxygenase-2 inhibitor, 5-LO inhibitor, and the immunosuppressive drug are identified in claim 9 by their ability to either selectively inhibit a particular enzyme or selectively function as an antiproliferating agent, an antiinflammatory or a leukocyte activation inhibitor, just as the inorganic salt in *In re Fuetterer* was described solely by its ability to maintain other components of the composition in "colloidal suspension." Based upon the recited function of each component of the claim 9 combination, a skilled artisan would discern that the applicants were in possession of the invention.

Similar to the combination of *In re Herschler*, claim 9 is directed to a composition employing the use of **three known classes** of chemical compounds: cyclooxygenase-2 selective inhibitors, 5-LO inhibitors, and immunosuppressive drugs. As a class, "selectivity" is defined functionally in the specification for these compounds such that a skilled artisan can readily distinguish members that belong to each class from those that do not (i.e. a "selective" compound from a non-selective compound) based upon the function of the particular compound irrespective of the chemistry it may possess. Moreover, in *In re Herschler*, claims were directed to "a physiologically active steroidal agent" as a class of chemical compounds where the specification detailed only 1 example. In the instant case, the specification provides over 15 examples of compounds that selectively inhibit cyclooxygenase-2, over 150 examples of selective 5-LO inhibitors, and over 11 examples of immunosuppressive drugs. If the CCPA determined that a functional description and one example satisfied the written description requirement, applicants' functional description plus 15, 150 and 11 examples which have the respective common attribute required in the claim, namely, selectivity for cyclooxygenase-2 and 5-LO and immunosuppressive functions, respectively cannot fairly be deemed to be a insufficient description.

In view of this comprehensive disclosure and relevant case law, one skilled in the art would discern that applicants were in possession of the combination detailed in the pending claims.

In view of the above, Applicants respectfully traverse this basis for rejection and request its reconsideration and withdrawal.

B. Enablement Rejection

Reconsideration is requested of the rejection of Claims 9-20 and 22-38 under 35 U.S.C.112, first paragraph as not sufficiently enabled by the specification.

Claim 9 is directed toward a composition comprising a **cyclooxygenase-2 inhibitor** (COX-2), a **5-lipoxygenase inhibitor** (5-LO) and an **immunosuppressive**

drug selected from antiproliferative agents, antiinflammatory-acting compounds and inhibitors of leukocyte activation. Claims 10-19 depend from claim 9.

Claim 20 is narrower in scope than claim 9, and is directed towards a pharmaceutical composition comprising a therapeutically-effective amount of a 5-lipoxygenase inhibitor, a cyclosporin compound and a cyclooxygenase-2 inhibitor selected from Dupont Dup 697, Talsho NS-398, meloxicam, flosulide and compounds of Formula I or a pharmaceutically acceptable salt of a compound having Formula I. Cyclosporin compound belongs to the group of immunosuppressive drugs. Claim 22-38 depend from claim 20.

A specification must be taken as in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for the enabling support. (See, e.g., *In re Marzocchi*, 439 F.2d 220, 223-4 (CCPA 1971); see also MPEP §2164.04). As a result, the burden rests on the Patent Office to establish a *prima facie* case of nonenablement, which requires the Office to provide acceptable evidence or reasoning inconsistent with the contested statements. (*Id.*; see also *In re Strahilevitz*, 668 F.2d 1229, 1232.) In this instance, the Office has failed to establish a *prima facie* case of nonenablement with respect to the invention as defined by the pending claims.

The standard for enablement is whether one of ordinary skill in the art could make or use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. See, e.g., U.S. v. Teletronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). In this case, the specification coupled with information generally known in the art, fully enables a skilled artisan to identify and prepare compositions for use in the present invention without undue experimentation.

The specification recites both functional and structural features that enable a skilled artisan to select suitable cyclooxygenase-2 inhibitors for use in the claimed

composition (see quotation at page 19 of this response). Similarly, the specification enables one of ordinary skill in the art to use 5-LO inhibitors and immunosuppressive drugs to prepare a composition of claim 9. See the above discussion regarding the structural and functional features of COX-2 inhibitors, 5-LO inhibitors, and immunosuppressive drugs.

Furthermore, the specification provides detailed guidance that fully enables a skilled artisan to prepare a cyclooxygenase-2 inhibitor employed in the combination of claim 9. More specifically, any one of reaction schemes I-X may be utilized to prepare a cyclooxygenase-2 inhibitor having formula I (see pages 27-40 of the specification). The specification further discloses 3 examples of compounds that were made following the steps of one of the reaction schemes. See pages 41-43 of the specification. In addition, the specification discloses well over 150 examples of available compounds exhibiting selective 5-LO inhibition (see pages 13-14 of the specification). The specification also discloses a number of classes of immunosuppressants that may be employed in the combination of claim 9 along with examples of specific compounds belonging to each class (see the discussion under the written description section).

The specification also details biological testing of an embodiment of the composition of claim 9 (and also claim 20) in a "transplantation and evaluation of graft rejection" model. See pages 43-45 of the specification.

Thus, a skilled artisan is fully empowered to make and use the combination of claim 9 without undue experimentation. Regarding claim 20, the combination of compounds described therein represents a subset of compounds of claim 9; however, claim 20 requires a pharmaceutical formulation rather than just a composition as is the case in claim 9. Applicants note that preparation and use of pharmaceutical compositions are described in detail on pages 45-49. The use of compounds of claim 20 is enabled for the same reason as the use of compounds of claim 9. Hence, claim 20 is enabled.

Furthermore, as stated in *In re Angstadt and Griffin*, 190 USPQ 218:

> Appellants have apparently not disclosed *every* catalyst which will work; they have apparently not disclosed *every* catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with *every* species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. (Original emphasis.)

The Office further cited In re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988)) in support of its enablement rejection. In the Wands case, the claim at issue required using an antibody "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^9 M^{-1}$." *Id.*, at 8 USPQ2d p. 1402. However, contrary to the Office's assertion, Wands supports the conclusion that claims 9 and 20 are enabled. Each of the factors considered by the Federal Circuit in the Wands case is discussed below. The factors are discussed with respect to claim 9 since, as mentioned above, compounds used in claim 20 represent a subset of compounds of claim 9.

With respect to the factor of the "amount of direction provided by the inventor," the Federal Circuit concluded that Wands provided "significant guidance and direction on how to practice the invention and present[ed] working examples." The Wands patent (4,879,219) is 18 columns long, including two columns of claims. The present specification is 49 pages long, excluding the claims. One skilled in the art, equipped with the detailed disclosure of the instant specification could readily prepare, select, and test compounds within the scope of claim 9. While some experimentation may be needed, such experimentation could be routinely performed by a skilled artisan, i.e. it would not be undue.

With regard to "the level of skill," the Federal Circuit stated "[T]here was a high level of skill in the art at the time when the application was filed." *ID.*, at 8 USPQ 2d

1406. In the present situation, the level of skill in pharmaceutical sciences and organic chemistry is similarly high.

With regard to "the nature of the invention," the Federal Circuit in Wands stated that

> the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Similarly in the present case, the nature of the invention requires reasonable screening of compounds and reasonable testing of the combinations of compounds disclosed in claim 9.

With regard to "working examples," the present specification provides 2 examples of COX-2 inhibitor synthesis, 1 example of 5-LO inhibitor synthesis, and 1 example for testing of the efficacy of combinations of 1) COX-2 inhibitor and 5-LO inhibitor, and 2) COX-2 inhibitor, 5-LO inhibitor and cyclosporin A.

With regard to "state of the art," the state of the art is especially well developed in the fields of chemical synthesis, screening for pharmaceutical activity, and drug testing.

With regard to the "breath of the claims," the Federal Circuit noted that of 143 candidate antibodies produced by Wands, his testing of just nine and proving the required activity of just four, not even considering countless others which Wands did not make, was sufficient to support claims of the following breadth: "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}." *ID.*, at 8 USPQ 2d 1405. This breadth, deemed acceptable, is much broader than a claim limited to those antibodies that Wands either produced or tested. Against this background, the breadth of claim 9 is reasonable in light of the detailed specification, which includes a number of synthetic schemes and working examples.

With regard to the "level of predictability," screening compounds according to the procedures in the specification and Example 4 is well within the ordinary skill in the art.

With regard to the "quantity of experimentation," in Wands 9 of 143 hybridomas were tested, and four were determined to have the required activity. This left 130+ hybridomas produced untested, as well as countless others not even produced. The present applicants should similarly not be precluded from patent protection on the basis they have left a considerable quantity of compounds untested, because, as stated by the Board in Ex parte Forman (230 USPQ 546, 547 (BPAI 1986); see also MPEP 2164.06):

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

In view of the foregoing, Applicants submit that claim 9 is sufficiently enabled. Hence, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 9. Applicants also note that claims 10-19 are dependent from claim 9, and are enabled for the same reasons as claim 9.

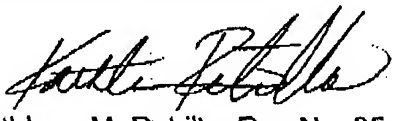
Furthermore, in view of the detailed discussion in the specification regarding the pharmaceutical compositions (see above) and the above discussion regarding the compounds of claim 9, Applicants also respectfully request reconsideration and withdrawal of the rejection of claim 20. Claims 22-38 depend from claim 20, and are enabled for the same reasons as claim 20.

III. Conclusion

In light of the foregoing, Applicants request withdrawal of claim rejections and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issue remain unresolved.

The Commissioner is hereby authorized to charge any deficiency or overpayment of the required fee to Deposit Account No. 19-1345.

Respectfully submitted,



Kathleen M. Petrillo, Reg No. 35,076
SENNIGER, POWERS, LEAVITT & ROEDEL
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

KMP/axs/lam